

Evaluation of a Multi-parameter Sensor for Automated, Continuous Cell Culture Monitoring in Bioreactors.

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Background: Compact and automated sensors are desired for assessing the health of cell cultures in biotechnology experiments in microgravity. Measurement of cell culture medium allows for the optimization of culture conditions on orbit to maximize cell growth and minimize unnecessary exchange of medium. While several discrete sensors exist to measure culture health, a multi-parameter sensor would simplify the experimental apparatus. One such sensor, the Paratrend 7, consists of three optical fibers for measuring pH, dissolved oxygen (pO_2), dissolved carbon dioxide (pCO_2), and a thermocouple to measure temperature. The sensor bundle was designed for intra-arterial placement in clinical patients, and potentially can be used in NASA's Space Shuttle and International Space Station biotechnology program bioreactors.

Methods: A Paratrend 7 sensor was placed at the outlet of a rotating-wall perfused vessel bioreactor system inoculated with BHK-21 (baby hamster kidney) cells. Cell culture medium (GTSF-2, composed of 40% minimum essential medium, 60% L-15 Leibovitz medium) was manually measured using a bench top blood gas analyzer (BGA, Ciba-Corning).

Results: A Paratrend 7 sensor was used over a long-term (>120 day) cell culture experiment. The sensor was able to track changes in cell medium pH, pO_2 , and pCO_2 due to the consumption of nutrients by the BHK-21 (See Figure 1 for a representative plot of sensor output). When compared to manually obtained BGA measurements, the sensor had good agreement for pH, pO_2 , and pCO_2 with bias [and precision] of 0.02 [0.15], 1 mm Hg [18 mm Hg], and -4.0 mm Hg [8.0 mm Hg] respectively. The Paratrend oxygen sensor was recalibrated (offset) periodically due to drift. The bias for the raw (no offset or recalibration) oxygen measurements was 42 mm Hg [38 mm Hg]. The measured response (rise) time of the sensor was 20 ± 4 s for pH, 81 ± 53 s for pCO_2 , 51 ± 20 s for pO_2 . For long-term cell culture measurements, these response times are more than adequate. Based on these findings, the Paratrend sensor could offer automated, continuous monitoring of cell cultures with a temporal resolution of 1 minute, which is not attainable by sampling via handheld blood analyzer (i-STAT).

Conclusion: The resulting bias and precision found in these cell culture-based studies is comparable to Paratrend sensor clinical results. Although the large error in pO_2 measurements (± 18 mm Hg) may be acceptable for clinical applications, where Paratrend values are periodically adjusted to a BGA measurement, the O_2 sensor in this bundle may not be reliable enough for the single-calibration requirement of sensors used in NASA's bioreactors. The pH and pCO_2 sensors in the bundle are reliable and stable over the measurement period, and can be used without recalibration to measure cell cultures in microgravity biotechnology experiments. Future work will test additional Paratrend sensors to provide statistical assessment of sensor performance.

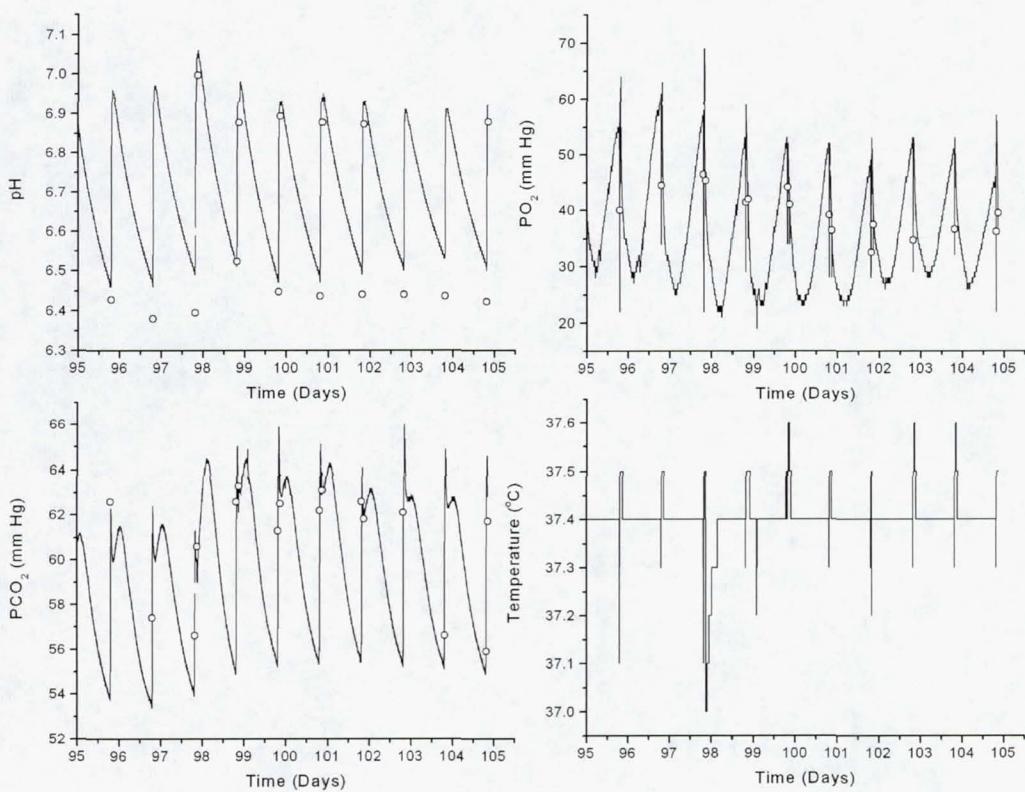


Figure 1: Typical data using BHK-21 cells in rotating bioreactor culture as measured by a Paratrend sensor (—) and a bench-top BGA (○). Cycles reflect daily infusion of fresh cell culture medium infusion into the bioreactor. The temperature dip on Day 98 is associated with changing medium bottles in the incubator.